Gut carbohydrate inhibits GIP secretion via a microbiota/SCFA/FFAR3 pathway

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Abstract
Mechanisms of carbohydrate-induced secretion of the two incretins namely glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are considered to be mostly similar. However, we found that mice exhibit opposite secretory responses in response to co-administration of maltose plus an α-glucosidase inhibitor miglitol (maltose/miglitol), stimulatory for GLP-1, as reported previously, but inhibitory for GIP. Gut microbiota was shown to be involved in maltose/miglitol-induced GIP suppression, as the suppression was attenuated in antibiotics (Abs)-treated mice and abolished in germ-free mice. In addition, maltose/miglitol administration increased plasma levels of short-chain fatty acids (SCFAs), carbohydrate-derived metabolites, in the portal vein. GIP suppression by maltose/miglitol was not observed in mice lacking a SCFA receptor Ffar3, but it was normally seen in Ffar2-deficient mice. Similar to maltose/miglitol administration, co-administration of glucose plus a sodium glucose transporter inhibitor phloridzin (glucose/phloridzin) induced GIP suppression, which was again cancelled by Abs treatment. In conclusion, oral administration of carbohydrates with α-glucosidase inhibitors suppresses GIP secretion through a microbiota/SCFA/FFAR3 pathway.

Introduction
Oral ingestion of carbohydrate triggers secretion of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), the major incretins that inhibit the rise in blood glucose levels by potentiating insulin secretion (Campbell & Drucker 2013, Nauck & Meier 2018). GLP-1 and GIP are secreted from enteroendocrine L-cells and K-cells, respectively, and both cell types are equipped with a sensing apparatus for luminal carbohydrates (Reimann & Gribble 2016, Svendsen & Holst 2016). The precise elucidation of the molecular mechanism of incretin secretion has long been hampered by the paucity and dispersed distribution of these cells in the gut villi. However, live visualization of these cells using a fluorescent protein in genetically engineered mice has greatly promoted the molecular and electrophysiological elucidation of L-cells (Reimann et al. 2008) and K-cells...
(Parker et al. 2009, Suzuki et al. 2013). Analyses of isolated primary L-cells have revealed that the cells are electrically excitable and glucose responsive. L-cells have been shown to express genes potentially involved in glucose-induced GLP-1 secretion, such as ATP-sensitive K-channel (K_ATP) subunits (Kir6.2 (Kcnj11) and SUR1 (Abcc8)), sodium-glucose transporter 1 (Sglt1 or Slc5a1), glucose transporter 2 (Glut2 or Slc2a2) and glucokinase (Gck). Functional involvement of these genes in the secretion has also been supported by other studies (Parker et al. 2012, Kuhre et al. 2015, Sun et al. 2017). Using the same technique, the molecular mechanism of GIP secretion, as well as that of GLP-1, has been studied in isolated primary K-cells, in which Kir6.2 and SUR1, Sglt1, Glut2 and Gck were shown to be expressed (Parker et al. 2009). Based on these reports, the mechanism of carbohydrate sensing and incretin secretion has been recognized to be similar in L-cells and K-cells.

We previously reported that carbohydrate-induced GLP-1 secretion was potentiated by either acarbose or miglitol, α-glucosidase inhibitors (α-GIs) that have been widely used for treatment of diabetes mellitus with the aim to suppress hydrolysis of poly-, oligo- and di-saccharides (Sakurai et al. 2012, Lee et al. 2015). Interestingly, we found that co-administration of maltose and miglitol evoked opposite effects on GLP-1 and GIP secretion: stimulatory for GLP-1 and inhibitory for GIP. In the present study, we examined the regulatory mechanism of carbohydrate-induced GIP secretion in detail.

Materials and methods

Reagents

Phloridzin, acarbose, metronidazole, neomycin and vancomycin were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Ampicillin was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Diprotin A was purchased from Peptide Institute, Inc. (Osaka, Japan). Miglitol was provided by Sanwa Kagaku Kenkyusho Co. Ltd. (Nagoya, Japan).

Animal experiments

WT mice, Kir6.2-deficient (Kir6.2−/−) mice that lack K_ATP channels (Miki et al. 1998), Ffar2-deficient (Ffar2−/−) mice (Kimura et al. 2013) and Ffar3-deficient (Ffar3−/−) mice (Kimura et al. 2011) all having a genetic background of C57BL/6J were used for the study. The mice were maintained on normal standard chow diet (CE-2) (12.1% kcal from fat) (CLEA Japan Inc., Tokyo, Japan). To deplete gut microbiota, the mice were treated with a combination of antibiotics (Abs) as previously described (Rakoff-Nahoum et al. 2004). Briefly, 8-week-old C57BL/6J mice were treated for 4 weeks with ampicillin (1 g/L), metronidazole (0.5 g/L) and neomycin (1 g/L) in the drinking water. Vancomycin (0.5 g/L) was included in the final 3 weeks of the treatment period. Germ-free (GF) mice (C57BL/6NJcl) were purchased from CLEA Japan Inc. GF mice were maintained in flexible film isolators in Research & Development Laboratories, Meiji Co. Ltd. (Hachioji, Japan). All animal studies were approved by the Animal Care and Use Committee of Chiba University, Tokyo University of Agriculture and Technology and Meiji Co. Ltd.

Meal tolerance test and meal-induced incretin secretion

Meal tolerance test (MTT) was performed by oral gavage of 10 μL/g (body weight) liquid formula (Ensure Liquid, Abbot Japan Co., Ltd, Tokyo, Japan) to WT mice fasted for 16 h. To monitor glucose excursion, blood glucose in the tail vein was measured at 0, 30, 60, 90 and 120 min after oral meal ingestion in awake mice. In independent experiments, meal-induced incretin secretion was measured by administering vehicle (distilled water), liquid formula or liquid formula containing miglitol (10 mg/kg) to 16-h-fasted WT mice. Thirty minutes after ingestion, the mice were anesthetized with isoflurane for 3 min and were laparotomized to collect portal vein blood, which was subjected to measurement of blood glucose, plasma GLP-1 and plasma GIP.

Carbohydrate-induced incretin secretion

After 16-h fasting, the mice were subjected to incretin secretion experiments. We collected blood samples at 5 min after glucose, according to the previous reports (Moriya et al. 2009), at 30 min after disaccharide (maltose) plus α-GI and at 30 min after glucose (2 g/kg) plus a SGLT-inhibitor phloridzin (500 mg/kg) administration (Lee et al. 2015). For assessing incretin secretion in response to various glucose doses, vehicle, glucose (0.2–2 g/kg) or maltose (2 g/kg) with or without α-GI (10 mg/kg for miglitol and 40 mg/kg for acarbose) was administered orally (10 μL/g), and portal vein samples were subjected to measurement of blood glucose, plasma GLP-1 and plasma GIP.
Measurement of GLP-1 and GIP

For measurement of GLP-1 and GIP in the blood, the blood sample was immediately mixed with EDTA (final 0.15% w/v) and Diprotin A (final 3 mmol/L). Concentrations of plasma GLP-1 and GIP were measured using glucagon-like peptide-1 (active) ELISA (Millipore) and Rat/Mouse GIP (total) ELISA (Millipore).

Measurement of SCFAs

To measure plasma SCFAs levels, the blood was drawn from the portal vein and plasma sample was separated by centrifugation and plasma levels of the SCFAs (acetate, propionate, butyrate, valerate, iso-butyrate and iso-valerate) in the portal vein were measured as previously described (Nakajima et al. 2017).

Statistics

Results are expressed as means ± s.e.m. Differences between two groups were assessed using the unpaired two-tailed Student’s t-test unless otherwise noted. Data sets involving more than two groups were assessed by one-way ANOVA or two-way ANOVA (GraphPad Prism software, version 7.0). P < 0.05 was considered statistically significant.

Results

αGI increased GLP-1 secretion, but decreased GIP secretion during MTT

To compare the secretion of two incretins, we measured incretin secretion in response to mixed meal in WT mice. Ten milligram per kilogram miglitol markedly lowered the glycemic excursion after liquid formula ingestion (Fig. 1A). In independent experiments, we measured blood glucose (Fig. 1B) and plasma GLP-1 (Fig. 1C) and GIP (Fig. 1D) levels in the portal vein of mice ingested with vehicle, liquid formula or liquid formula plus miglitol. Notably, meal-induced GLP-1 secretion was increased by miglitol (Fig. 1C), while GIP secretion was markedly decreased (Fig. 1D). Since carbohydrate-induced GIP secretion was reported to be dose dependent in humans (Pilchiewicz et al. 2007) and in rats (Yoder et al. 2010), the reduction in meal-induced GIP secretion by miglitol would be explained by the reduction in absorbable glucose due to α-glucosidase inhibition with miglitol. Therefore, we first assessed the relationship between the dose of oral glucose loads and portal GIP concentrations in our experimental condition in mice.

KATP Channel is not essential for glucose-induced GIP secretion

WT mice were administered orally with variable doses (0, 0.2, 0.5, 1 and 2 g/kg) of glucose, and the levels of blood glucose and plasma GLP-1 and GIP in the portal vein were measured 5 min after ingestion. There was a significant increase in the levels of blood glucose (Fig. 2A), GLP-1 (Fig. 2B) and GIP (Fig. 2C) in response to various glucose doses. The minimum dose for the statistically significant increase in blood glucose, GLP-1 and GIP in WT mice was 0.2, 1 and 0.5 g/kg, respectively. We also examined physiological relevance of KATP channels in dose-dependent incretin secretion by using Kir6.2−/− mice that systemically lack the KATP channel (Miki et al. 1998). We previously reported that glucose could induce secretion of GIP (Miki et al. 2005) and GLP-1 (Lee et al. 2015) in the absence of KATP channels using a relatively large dose of glucose (~6 g/kg for GIP and 2 g/kg for GLP-1). In the present study, using a physiological range of glucose and portal vein samples, we found that the blood glucose levels (Fig. 2A) and the secretion of GLP-1 (Fig. 2B) and GIP (Fig. 2C) in Kir6.2−/− mice were not

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different from those in WT mice. Especially, there is a correlation between postprandial blood glucose levels and postprandial plasma GIP levels in both WT and Kir6.2−/− mice with higher correlation coefficient (WT, r = 0.839; Kir6.2−/−, r = 0.792) compared with that of GLP-1 (WT, r = 0.535; Kir6.2−/−, r = 0.432) (Fig. 2D and E), suggesting that K\textsubscript{ATP} channels are not essential for glucose-induced GIP secretion.

**Maltose-induced GIP secretion was significantly inhibited by α-GIs**

In addition to carbohydrates, lipids and proteins in mixed meal trigger GIP secretion. Therefore, the mechanism of the GIP suppression by miglitol would better be examined by administering carbohydrates alone. We used a di-saccharide maltose, instead of mixed meal, examined by administering carbohydrates alone. We previously reported that miglitol potentiates maltose-induced GLP-1 secretion by activating SGLT3 (Lee et al. 2015). In accord with this report, administration of maltose and acarbose, another α-GI having no effect on SGLT3, significantly increased GLP-1 secretion (\(P = 1.7 \times 10^{-6}\)), but the increase was significantly smaller than that of maltose/miglitol (\(P = 0.0016\)) (Fig. 3B). However, contrary to the effect of SGLT3 on GLP-1 secretion, GIP secretion was similarly reduced (\(P = 0.0097\)) also by maltose/acarbose (Fig. 3C), suggesting that the reduced GIP secretion by miglitol is mediated by its property as a blocker of α-glucosidase. Suppression of GIP secretion by oral administration of maltose/miglitol could be due to inhibition of glucose absorption in the upper small intestine and the supply of glucose in the lower. To test this possibility, glucose was infused directly into the mid small intestine and blood glucose and plasma GLP-1 and GIP but not GLP-1 levels (Supplementary Fig. 1A, B and C, see section on supplementary data given at the end of this article). We previously reported that miglitol potentiates maltose-induced GLP-1 secretion by activating SGLT3 (Lee et al. 2015). In accord with this report, administration of maltose and acarbose, another α-GI having no effect on SGLT3, significantly increased GLP-1 secretion (\(P = 1.7 \times 10^{-6}\)), but the increase was significantly smaller than that of maltose/miglitol (\(P = 0.0016\)) (Fig. 3B). However, contrary to the effect of SGLT3 on GLP-1 secretion, GIP secretion was similarly reduced (\(P = 0.0097\)) also by maltose/acarbose (Fig. 3C), suggesting that the reduced GIP secretion by miglitol is mediated by its property as a blocker of α-glucosidase.

**SCFAs suppress GIP secretion via FFAR3**

In conclusion, GLP-1 secretion was not altered by administration of SCFAs (maltose/miglitol or maltose/acarbose) (\(P < 0.05\), **\(P < 0.01\), ***\(P < 0.001\)) (Supplementary Fig. 2A, B and C). For this aim, overnight-fasted mice were anesthetized with isoflurane and laparotomized. The gut was then, tied and cut off in the mid small intestine (at 15 cm proximity from the terminal ileum) and portal vein at 30 min after oral administration of SCFAs (maltose/miglitol or maltose/acarbose) (\(n = 24–28\)). **\(P < 0.01\), ***\(P < 0.001\) by one-way ANOVA with Tukey’s post hoc analysis. (A, B and C) Data are means ± s.e.m. (D and E) Scatter plots between blood glucose and plasma GLP-1 (D) or GIP (E) of WT (filled circles) and Kir6.2−/− (open circles) mice.

**Figure 2**

Incretin secretory response to a variable dose of glucose. (A, B, C and E) Blood glucose (A), plasma GLP-1 (B) and plasma GIP (C) in the portal vein at 5 min after oral administration of a variable dose of glucose to WT (filled columns) and Kir6.2−/− (open columns) mice are shown (\(n = 10–15\)). **\(P < 0.01\), ***\(P < 0.001\), and ***\(P < 0.001\) vs vehicle administration by one-way ANOVA with Tukey’s post hoc analysis. (A, B and C) Data are means ± s.e.m. (D and E) Scatter plots between blood glucose and plasma GLP-1 (D) or GIP (E) of WT (filled circles) and Kir6.2−/− (open circles) mice.

**Figure 3**

Effect of α-GIs on maltose-induced incretin secretion in WT mice. (A, B and C) Blood glucose (A), plasma GLP-1 (B) and plasma GIP (C) in the portal vein at 30 min after oral administration of vehicle, maltose/miglitol or maltose/acarbose (\(n = 24–28\)). **\(P < 0.01\), ***\(P < 0.001\) by one-way ANOVA with Tukey’s post hoc analysis. (A, B and C) Data are means ± s.e.m.
ileum), according to the previous report (Moriya et al. 2009). From the resection stump, glucose (2 g/kg) or vehicle (distilled water) was infused into the lower small intestine and the portal blood sample was drawn at 5 min after loading. While there was an apparent increase in plasma levels of GLP-1, the increases of blood glucose and plasma GIP were blunted, when compared with those during oral glucose loading (Fig. 2A and C). Nevertheless, plasma GIP levels were significantly increased and not decreased by glucose administration into the mid small intestine, suggesting that the GIP suppression by maltose/miglitol is unlikely to be due to decreased glucose availability in the upper small intestine.

In addition, the blunted increase in blood glucose and plasma GIP by maltose/miglitol administration would be induced by the GLP-1-mediated inhibition of gastric emptying. We then measured intestinal transit using Evans blue and found that intestinal transit was not suppressed by miglitol at least in our experimental condition (Supplementary Fig. 3A and B). Nevertheless, these results do not exclude the possibility that the suppression of intestinal transit may affect blood glucose and plasma GIP levels after maltose/miglitol administration. Furthermore, administration of miglitol alone failed to affect GIP secretion (Supplementary Fig. 1A, B and C). All these results suggested that the retention of undigested maltose in the gut lumen may contribute to the maltose/miglitol-induced GIP suppression through a mechanism that does not require maltose utilization by the mice.

**Gut microbiota is involved in the suppression of GIP secretion by maltose/miglitol**

Gut microbiota utilize dietary carbohydrates as an energy source and release various metabolites into the gut lumen. Considering that the suppression of GIP secretion by maltose/miglitol is mediated by the gut microbiota, we induced gut dysbiosis by administering a combination of Abs to the mice for 4 weeks and measured blood glucose and plasma GLP-1 and GIP levels (Fig. 4A, B and C). As reported previously, 4-week treatment with Abs induced marked enlargement of the cecum and the gallbladder (Supplementary Fig. 4A, B and C). GIP secretion by maltose/miglitol was significantly decreased below basal (vehicle administration) level in Abs-untreated mice (Fig. 4C). However, the reduction in GIP secretion by maltose/miglitol in Abs-treated mice was significantly smaller than that in Abs-untreated mice ($P=0.0074$). Since Abs treatment is considered not to completely abolish microbiota, we repeated the same experiments in GF mice (Fig. 4D, E and F). In the GF mice, the reduction in GIP secretion by maltose/miglitol was absent, suggesting that the GIP suppression is dependent on microbiota.
By contrast, plasma GLP-1 levels under unstimulated condition were markedly elevated in the Abs-treated (Fig. 4B) and GF mice (Fig. 4E). The increase in GLP-1 levels by maltose/miglitol was relatively small (1.38 fold in Abs (+) vs 3.9 fold in Abs (−)) in Abs-treated mice (Fig. 4B) and absent in the GF mice (Fig. 4E).

SCFA/FFAR3 pathway is involved in maltose/miglitol-induced GIP suppression

Fermentation of dietary carbohydrates by gut microbiota gives rise to production of short-chain fatty acids (SCFAs), which was reported to stimulate GLP-1
secretion through binding to their receptors including FFAR2 (GPR43) (Tolhurst et al. 2012). By contrast, the relationship between SCFAs and GIP secretion remains mostly unknown. We hypothesized that SCFAs generated from maltose by gut microbiota might inhibit the GIP secretion when maltose was co-administered with miglitol. We first measured plasma SCFA levels in the portal vein at 30 min after administration of vehicle, maltose (2 g/kg) alone or miglitol (10 mg/kg) alone. Administration of maltose alone did not affect SCFA levels. In addition, administration of miglitol alone increased plasma acetate, but there was no statistically significant increase in the other SCFAs (Supplementary Fig. 1D, E, F, G, H and I). As expected, when maltose was co-administered with miglitol, we found that SCFAs in the portal vein were significantly increased (Fig. 5A, B, C, D, E and F). In addition, 4-week treatment with Abs markedly reduced basal (vehicle) plasma SCFA levels and their increase by maltose/miglitol administration, both of which are considered to reflect the decrease in microbiota by Abs treatment. We then examined the involvement of SCFA receptors in maltose/miglitol-induced GIP suppression by using mice lacking FFAR2 (Ffar2−/−) (Fig. 5G, H and I) or its isoform FFAR3 (Ffar3−/−) (Fig. 5J, K and L).

In Ffar2−/− mice, maltose/miglitol suppressed GIP secretion similarly to its effect in WT mice (Fig. 5I), indicating that FFAR2 is not essential for maltose/miglitol-induced GIP suppression. Notably, in Ffar3−/− mice, GIP secretion was not suppressed by maltose/miglitol (Fig. 5L), indicating that FFAR3 is essential for maltose/miglitol-induced GIP suppression. However, there was no remarkable change in GLP-1 secretion in Ffar2−/− and Ffar3−/− mice (Fig. 5H and K).

**Figure 6**

Effect of blockade of glucose absorption on GIP secretion. (A, B and C) Blood glucose (A), plasma GLP-1 (B) and plasma GIP (C) in the portal vein at 30 min after oral administration of vehicle (open columns) or glucose/phloridzin (filled columns) to WT mice with (Abs (+)) or without (Abs (−)) Abs treatment (n=8−15). (D, E, F, G, H and I) Plasma SCFAs (acetate (D), propionate (E), n-butyrate (F), n-valerate (G), iso-butyrate (H) and iso-valerate (I)) in the portal vein at 30 min after oral administration of vehicle or glucose/phloridzin (n=8−10) to WT mice with (Abs (+)) or without (Abs (−)) Abs treatment. NS, not significant, *P<0.05, **P<0.01, and ***P<0.001 by two-way ANOVA plus Tukey’s post hoc analysis (A, B, C, D, E, F, G, H and I). (A, B, C, D, E, F, G, H and I) Data are means±S.E.M.
Blockade of glucose absorption, as well as inhibition of maltose hydrolysis, inhibits GIP secretion through a microbiome-dependent mechanism

We next examined whether intra-intestinal retention of glucose, instead of maltose, and its utilization by gut microbiota is required for the GIP suppression. For this aim, we co-administered glucose and an antagonist of the sodium glucose transporter (SGLT) phloridzin (glucose/phloridzin) and measured blood glucose (Fig. 6A) and plasma GLP-1 (Fig. 6B) and GIP (Fig. 6C). As expected, glucose/phloridzin significantly suppressed GIP secretion (Fig. 6C), possibly through a mechanism similar to that induced by maltose/miglitol. Therefore, we examined the GIP secretion by glucose/phloridzin in Abs-treated mice and found that GIP secretion was not suppressed by glucose/phloridzin (Fig. 6C), suggesting the involvement of the gut microbiota.

Furthermore, SCFAs in the portal vein were found to be increased at 30 min after glucose/phloridzin administration (Fig. 6D, E, F, G, H and I) in Abs-untreated mice, indicating that SCFAs can be produced acutely after a single oral carbohydrate administration when it is co-administered with α-GIs. In addition, Abs treatment markedly reduced SCFA increase by glucose/phloridzin administration (Fig. 6D, E, F, G, H and I).

Discussion

Trillions of bacterial flora reside in the gut of humans and rodents, and hosts and gut microbiota comprise an ecosystem of mutual symbiotic relationship (Lynch & Pedersen 2016, Schroeder & Backhed 2016). Gut microbiota have long been known to contribute to various biological processes of the hosts, including protection against harmful pathogen overgrowth, fat absorption through bile acid metabolism, replenishment of several vitamins and fueling gut epithelium through utilization of indigestible fibers. In addition to these well-known functions, recent studies have clarified critical roles of gut microbiota in the regulation of metabolic disorders, such as obesity, insulin resistance and diabetes mellitus (Ridaura et al. 2013, Suez et al. 2014, Forslund et al. 2015).

The physiological roles of gut microbiota on incretin secretion was demonstrated by several findings; dietary supplementation with fermentable fibers increased GLP-1 levels (Zhou et al. 2008) and SCFAs stimulated GLP-1 secretion from primary isolated L-cells (Tolhurst et al. 2012). By contrast, basal GLP-1 levels in GF mice were found to be markedly elevated despite the low plasma SCFA levels in these mice (Wichmann et al. 2013). Accordingly, there still remains controversy about the role of gut microbiota in GLP-1 secretion.

Compared with these findings on GLP-1 secretion, the involvement of gut microbiota in GIP secretion is less clarified. In the present study, we found that GIP secretion was significantly suppressed by maltose/miglitol through a mechanism involving gut microbiota. We found that glucose-induced GIP secretion is independent of K$_{ATP}$ channel function. Accordingly, the apparent reduction in GIP by maltose/miglitol despite the small but significant increase in blood glucose prompted us to investigate the mechanism of this GIP suppression further. Because inhibition of maltose hydrolysis by miglitol resulted in the suppression of GIP secretion, we surmised that gut microbiota and bacterial metabolites should be involved. Importantly, our results on Ffar2$^{-/-}$ and Ffar3$^{-/-}$ mice suggested that SCFAs generated from oligosaccharides by gut microbiota suppress GIP secretion through their action on FFAR3 but not on FFAR2. Accordingly, FFAR3 was found to play a critical role in SCFA-induced GIP suppression. Recently, Ffar3 as well as Ffar2 have been
reported to be expressed in K-cells (Iwasaki et al. 2015). It has been reported that FFAR2 couples to Gi and Gq, while FFAR3 couples only to Gi. Therefore, activity of FFAR3 by SCFAs might suppress GIP secretion through lowering intracellular cAMP levels in K-cells (Fig. 7).

Since GIP has been exerted to pro-adipogenic action in adipose tissues (Miyawaki et al. 2002, Thondam et al. 2017), excessive secretion of GIP is undesirable in diabetes patients with obesity (Reimann & Gribble 2016). As α-GIs suppress an adipogenic hormone, GIP, but potentiate an anorexigenic hormone, GLP-1, the treatment of diabetes mellitus with α-GIs might be beneficial for obese diabetic patients to prevent further increase in their body weight. In accord with this, in several human studies, α-GIs have been reported to reduce the body weight of patients with diabetes mellitus (Sugimoto et al. 2015).

In conclusion, by analyzing carbohydrate-induced GIP secretion in mice, we have found that the inhibition of hydrolysis of carbohydrates by α-GIs in the gut reduces GIP secretion through a microbiota/SCFA/FFAR3 pathway.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/JOE-18-0241.

Declarations of interest
Two authors (K F and T J) are employed by Sanwa Kagaku Kenkyusho Co., Ltd., by which miglitol was provided. The authors declare that there is no other conflict of interest.

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